IFW

Docket No. BULK 3.0-018

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Manne Satyanarayana REDDY, *et al.*

Group Art Unit: 1624

Examiner: P.V. Ward

Application No.: 10/601,844

Filed: June 23, 2003

For: AMORPHOUS LEVOCETIRIZINE DIHYDROCHLORIDE

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

TRANSMITTAL LETTER

To complete the requirements of the priority claim under 35 U.S.C. § 119 for the subject application, applicants are submitting herewith a certified copy of India Patent Application No. 472/MAS/2002, filed June 22, 2002.

If there are any questions regarding this submission, please contact the undersigned.

Respectfully submitted

Dated: September 18, 2006

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Filing Date: June 23, 2003
First Inventor: Manne Satyanarayana REDDY
Art Unit: 1624

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Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper. Documents enclosed:

Transmittal Letter - 1 page
Certified copy of India Application No. 472/MAS/2002 (14 pages)
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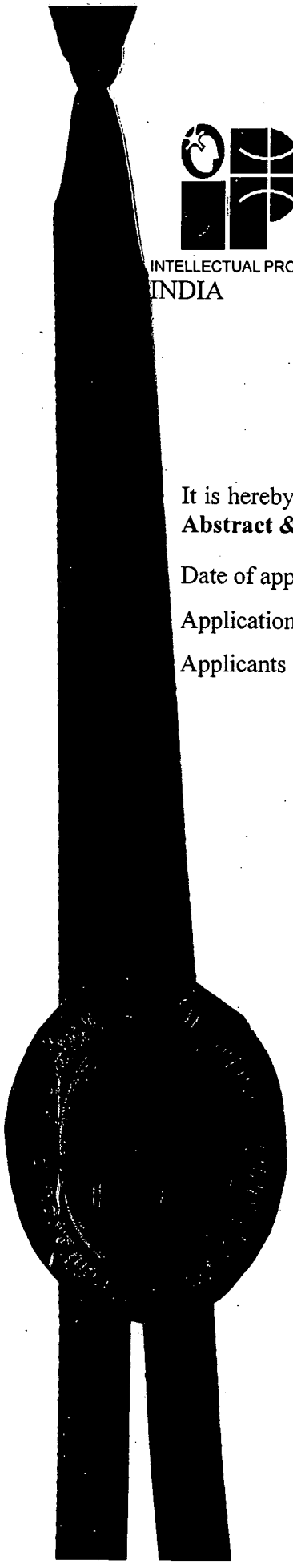

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It is hereby certified that annexed here to is a true copy of **Complete Specification, Abstract & Drawing** of the patent application as filed and detailed below:-

Date of application : **21-06-2002**

Application No : **472/MAS/2002**

Applicants : **Dr. Reddy's Laboratories Limited, an Indian Company having its registered office at 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh, India**

In witness there of
I have here unto set my hand

Dated this the 29th day of August 2006
7th day of Bhadrapada, 1928(Saka)

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FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION
(SECTION 10)

Novel Amorphous Form of

(-)-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid dihydrochloride

(LEVO CETIRIZINE DIHYDROCHLORIDE)

Dr. Reddy's Laboratories Limited,
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7-1-27, Ameerpet,
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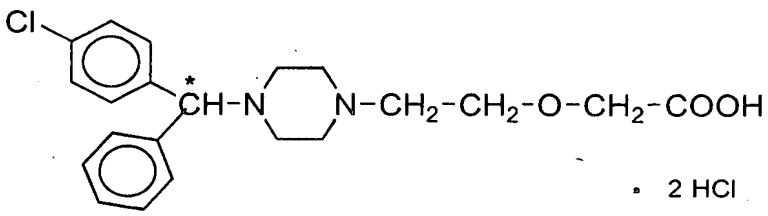
The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to novel amorphous form of (-)- [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid dihydrochloride. It is generically known as Levo Cetirizine dihydrochloride.

The present invention also relates to the process for the preparation of novel amorphous form of Levo Cetirizine dihydrochloride, which can be depicted as Formula (1).



Formula (I)

BACKGROUND OF THE INVENTION

Levo Cetirizine dihydrochloride is used for the treatment of allergic syndromes such as chronic and acute allergic rhinitis, allergic conjunctivitis, pruritus, urticaria etc. The product was proved to be remarkably free from side effects on the central nervous system.

GB 2 225 321 A discloses the process for the preparation of Levo Cetirizine dihydrochloride, which comprises treating the Levo Cetirizine with hydrochloric acid in acetone.

Tetrahedron Letters 37(28), 4837-4840 1996 journal which discloses the enantio selective synthesis of Levo Cetirizine dihydrochloride and further purification via ion exchange chromatography.

Many of the related patents were disclosed the process for the preparation of Levo Cetirizine and its salts including dihydrochloride in various methods, but none of these patents were described the existence of an amorphous form of Levo Cetirizine or its dihydrochloride.

It has been disclosed earlier that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms [Konne T., Chem. Pharm. Bull. 38, 2003 (1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. An amorphous form of Cefuroxime axetil is a good example for exhibiting higher bioavailability than the crystalline form.

During our laboratory experimentation as a part of process development, novel amorphous form of Levo Cetirizine dihydrochloride was resulted while crystallizing the Levo Cetirizine pharmaceutically acceptable salts in different solvents.

Hence, the main aspect of the present invention is to provide novel amorphous form of Levo Cetirizine dihydrochloride. The invention also provides the process for the preparation of novel amorphous form of Levo Cetirizine dihydrochloride.

The novel amorphous form of Levo Cetirizine dihydrochloride was characterized by X-ray powder diffractogram, which is not having well-resolved peaks.

The process for the preparation of novel amorphous form of the present invention is simple, eco-friendly and easily scalable.

SUMMARY OF INVENTION

The present invention relates to the novel amorphous of Levo Cetirizine dihydrochloride.

The present invention also relates to the process for the preparation of novel amorphous form of Levo Cetirizine dihydrochloride. The process for the preparation of amorphous form of

Levo Cetirizine dihydrochloride comprises the dissolution of Levo Cetirizine in an aqueous mixture of water miscible or immiscible solvent using hydrochloric acid and further isolation by adding water immiscible aromatic or aliphatic hydrocarbon solvents.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Fig-1 is a diagram showing the X-ray powder diffraction of amorphous form of Levo Cetirizine dihydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel amorphous form of Levo Cetirizine dihydrochloride.

The present invention also provides a process for preparing novel amorphous form of Levo Cetirizine dihydrochloride.

The present invention of amorphous form of Levo Cetirizine dihydrochloride was characterized by X-ray powder diffractogram. The X-ray powder diffraction pattern of amorphous form of Levo Cetirizine dihydrochloride was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The amorphous Form of Levo Cetirizine dihydrochloride of the present invention is having the X-ray powder diffractogram pattern substantially as depicted in Figure (1).

The novel amorphous form of (-)-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid dihydrochloride (Levo Cetirizine dihydrochloride) of the present invention is prepared by a process, which comprises,

a. dissolving the Levo Cetirizine in water and ketone solvents such as acetone, methyl ethyl ketone or 2-pentanone or mixture there of preferably acetone or in an aqueous mixture of water miscible solvents like C1-C5 straight or branched chain alcoholic sovents such as methanol, ethanol, n-propanol, isopropanol,

2- butanol, n-butanol, n-pentanol or 2-pentanol, preferably isopropanol or nitrile solvents such as acetonitrile or propionitrile, preferably acetonitrile or water immiscible aromatic or aliphatic or alicyclic hydro carbon sovents such as toluene, xylene, cyclohexane or heptane, preferably toluene;

b. adding the hydrochloric acid to reaction mixture of step(a);

c. distilling off the solvent from reaction solution of step (b);

d. addition of water immiscible aromatic or aliphatic or alicyclic hydrocarbon solvents such as toluene, xylene, cyclohexane or heptane, preferably cyclohexane to the compound obtained in step(c);

e. filtering the compound obtained in step (d);

f. drying the compound obtained in step (e) at a temperature of 80-120^{O}C to afford the desired amorphous form of Levo Cetirizine dihydrochloride.

The amorphous form of the present inventive substance is having moisture content varying from 0.3 to 12.0% by KF method usually the moisture content of the substance is having around 1.5 to 7.5 % by KF method.

The moisture content of present inventive substance was measured on Mettler DL-35 instrument using Karl-Fischer reagent.

The present inventive substance is thermally stable; hence it may be well suited for pharmaceutical formulations.

Hence, the present invention is directed to provide novel amorphous form of Levo Cetirizine dihydrochloride. The process for the preparation of present invention is simple, eco-friendly and commercially viable.

It is noteworthy to mention that the process of the Levo Cetirizine or its pharmaceutical acceptable salts was disclosed in prior art references known in the art. Levo Cetirizine or its pharmaceutical acceptable salts including dihydrochloride can also be outsourced in commercial quantities.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

Reference Example:

Preparation of Levo Cetirizine:

(+)-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethanol (105 grams) was dissolved in dimethyl formamide (357 ml) and cooled the reaction mixture to a temperature of 0-5 ° C. Potassium hydroxide (53.3 grams) was added to reaction mixture and maintained for 90 minutes. Then Sodium monochloroacetate (55.5 grams) was added and further maintained at a temperature of 0-5°C for 90 minutes. The temperature of reaction mixture was raised to 30-35 ° C and maintained till the reaction substantially completes. Water (1155 ml) was added to the reaction mixture and pH of the reaction mixture was adjusted to 9.5 to 9.8 with hydrochloric acid. Then the reaction mixture was washed with ethyl acetate (760 ml) and separated the layers. The pH of the aqueous layer was adjusted to 4 to 4.5 with Hydrochloric acid and extracted with dichloromethane (875 ml). The extracted Organic layer was washed with 10% Sodium chloride solution and followed by water. The solvent was distilled off from the reaction solution to afford Levo Cetirizine (Weight: 123.0 grams).

Preparation of novel amorphous Form of Levo Cetirizine dihydrochloride:

Example 1:

Levo Cetirizine (5 grams) was dissolved in a mixture of water (20 ml) and acetone (50 ml) at the room temperature. Hydrochloric acid (5 ml) was added to reaction mixture and stirred for 10 to 30 min at a temperature of 30 to 35 ° C. Then, the reaction solution was filtered and distilled off the solvent completely to dryness at a temperature of below 80 ° C. Cyclohexane (50 ml) was added to the residual mass and stirred for 30 minutes at a temperature of 30-35°C. The obtained product was filtered and washed with cyclohexane (25 ml) and on subsequent drying at a temperature of 60-110 ° C to a constant weight resulted the novel amorphous form of Levo Cetirizine dihydrochloride.

(Weight: 4.7 grams, M.C by KF: 1.7%)

Example-2:

Levo Cetirizine (10.0 grams) was taken in a mixture of toluene (100 ml) and water (50 ml), Concentrated hydrochloric acid solution (10 ml) was added and stirred to get the clear solution. Then, the reaction solution was filtered and distilled off the solvent completely to dryness at a temperature of 70-90 ° C under vacuum. Toluene (100 ml) was added to the residual mass and stirred for 30 minutes at a temperature of 30-35 ° C. The obtained compound was filtered, washed with toluene (50 ml) and on subsequent drying at a temperature of 60-65 ° C to a constant weight resulted the novel amorphous form of Levo Cetirizine dihydrochloride

(Weight: 9.4 grams, M.C by KF: 4.0%)

Example -3:

Levo Cetirizine (10.0 grams) was taken in a mixture of acetonitrile (100 ml) and water (50 ml), Concentrated hydrochloric acid solution (6.0 ml) was added and stirred to get the clear solution. Then, the reaction solution was filtered and distilled off the solvent completely to dryness at a temperature of 70-80^{O}C under vacuum to result amorphous form of Levo Cetirizine dihydrochloride.

(Weight: 12.0 grams; M.C by KF: 2.3%)

Example-4:

Levo Cetirizine dihydrochloride (10.0 grams) was dissolved in a mixture of acetone (40 ml) and water (100 ml) further the reaction mixture was stirred at a temperature of 25-35^{O}C to get a clear solution. The reaction solution was filtered and solvent was distilled off from the reaction solution completely to dryness at a temperature of 50-75^{O}C under reduced pressure to result the amorphous form of Levo Cetirizine dihydrochloride. The amorphous form of Levo Cetirizine dihydrochloride was further dried at a temperature of 70-75 ^{o}C to a constant weight to afford the novel amorphous form of Levo Cetirizine dihydrochloride.

(Weight: 9.4 grams; M.C by KF: 5.8%).

Example-5:

Levo Cetirizine dihydrochloride (10.0 grams) was dissolved in water (30 ml) at a temperature of 25-35^{O}C. Toluene (100 ml) was added to the reaction solution and distilled off the solvent completely to dryness from the reaction solution at a temperature of 60-80^{O}C. Then cyclohexane (200 ml) was added to the residual mass and stirred for 45-60 minutes at a temperature of 25-35^{O}C to crystallize the solid mass. The separated solid was filtered, washed

with cyclohexane (50 ml) and on subsequent drying at a temperature of 60-70^{O}C to a constant weight resulted the amorphous form of Levo Cetirizine dihydrochloride

(Weight: 9.6 grams; M.C by KF 3.5%).

Example-6:

Levo Cetirizine dihydrochloride (15.0 grams) was dissolved in water (15 ml) at a temperature of 25-35^{O}C. Isopropanol (150 ml) was added to the reaction solution and distilled off the solvent completely to dryness from the reaction solution at a temperature of 70-80^{O}C.

Then di isopropyl ether (300 ml) was added to the residual mass and stirred for 45-60 minutes at a temperature of 25-35^{O}C to crystallize the solid mass. The separated solid was filtered, washed with di isopropyl ether (75 ml) and on subsequent drying at a temperature of 60-75^{O}C to a constant weight resulted the novel amorphous form of Levo Cetirizine dihydrochloride

(Weight: 14.8 grams; M.C by KF 4.6%).

The XRD pattern of the Levo Cetirizine dihydrochloride obtained from the above examples are similar, which are not having well resolved peaks.

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig.1 is characteristic X-ray powder diffraction pattern of novel amorphous form of Levo Cetirizine dihydrochloride.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

It shows a plain halo with no peaks, which is characteristic of the amorphous nature of product.

We claim:

1. A novel amorphous form of (-)-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride (Levo Cetirizine dihydrochloride).
2. The novel amorphous form of Levo Cetirizine dihydrochloride of claim 1 which is characterized by Powder X-ray diffractogram.
3. The amorphous form of Levo Cetirizine according to claim 1 and 2, which provides X-ray powder diffraction pattern substantially in accordance with Figure (1).
4. The amorphous form of Levo Cetirizine dihydrochloride of claim 1, which is having moisture content varying from 0.3 to 12.0% by KF method.
5. The amorphous form of Levo Cetirizine dihydrochloride of claim 1 and 4, which is having moisture content from 1.5 to 7.5 % by KF method.
6. A process for the preparation of novel amorphous form of (-)-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid dihydrochloride (Levo Cetirizine dihydrochloride), which comprises,

   a. dissolving the Levo Cetirizine in water and ketone solvents such as acetone, methyl ethyl ketone or 2-pentanone or mixture there of preferably acetone or in an aqueous mixture of water miscible solvents like C1-C5 straight or branched chain alcoholic sovents such as methanol, ethanol, n-propanol, isopropanol, 2-butanol, n-butanol, n-pentanol or 2-pentanol, preferably isopropanol or nitrile solvents such as acetonitrile or propionitrile, preferably acetonitrile or water immiscible aromatic or aliphatic or alicyclic aliphatic hydro

carbon sovents such as toluene, xylene, cyclohexane or heptane, preferably toluene;

b. adding the hydrochloric acid to reaction mixture of step(a);

c. distilling off the solvent from reaction solution of step (b);

d. addition of water immiscible aromatic or aliphatic or alicyclic hydrocarbon solvents such as toluene, xylene, cyclohexane or heptane, preferably cyclohexane to the compound obtained in step(c);

e. filtering the compound obtained in step (d);

f. drying the compound obtained in step (e) at a temperature of 80-120^{O}C to afford the desired amorphous form of Levo Cetirizine dihydrochloride.

7. The process according to step (a) of claim 6, wherein the said alcoholic solvent is isopropanol.

8. The process according to step (a) of claim 6, wherein the said ketone solvent is acetone.

9. The process according to step (a) of claim 6, wherein the said nitrile solvent is acetonitrile.

10. The process according to step (d) of claim 6, wherein the said alicyclic hydrocarbon solvent is cyclohexane

11. The process for the preparation of novel amorphous form of Levo Cetirizine dihydrochloride substantially as here in described and exemplified.

Dated this 20th day of June 2002

Signed)_____

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr.Reddy's Laboratories Limited.

ABSTRACT

The present invention relates to the novel amorphous of Levo Cetirizine dihydrochloride. The present invention also relates to the process for the preparation of novel amorphous form of Levo Cetirizine dihydrochloride. The process for the preparation of amorphous form of Levo Cetirizine dihydrochloride comprises the dissolution of Levo Cetirizine in an aqueous mixture of water miscible or immiscible solvent using hydrochloric acid and further isolation by adding water immiscible aromatic or aliphatic hydrocarbon solvents.

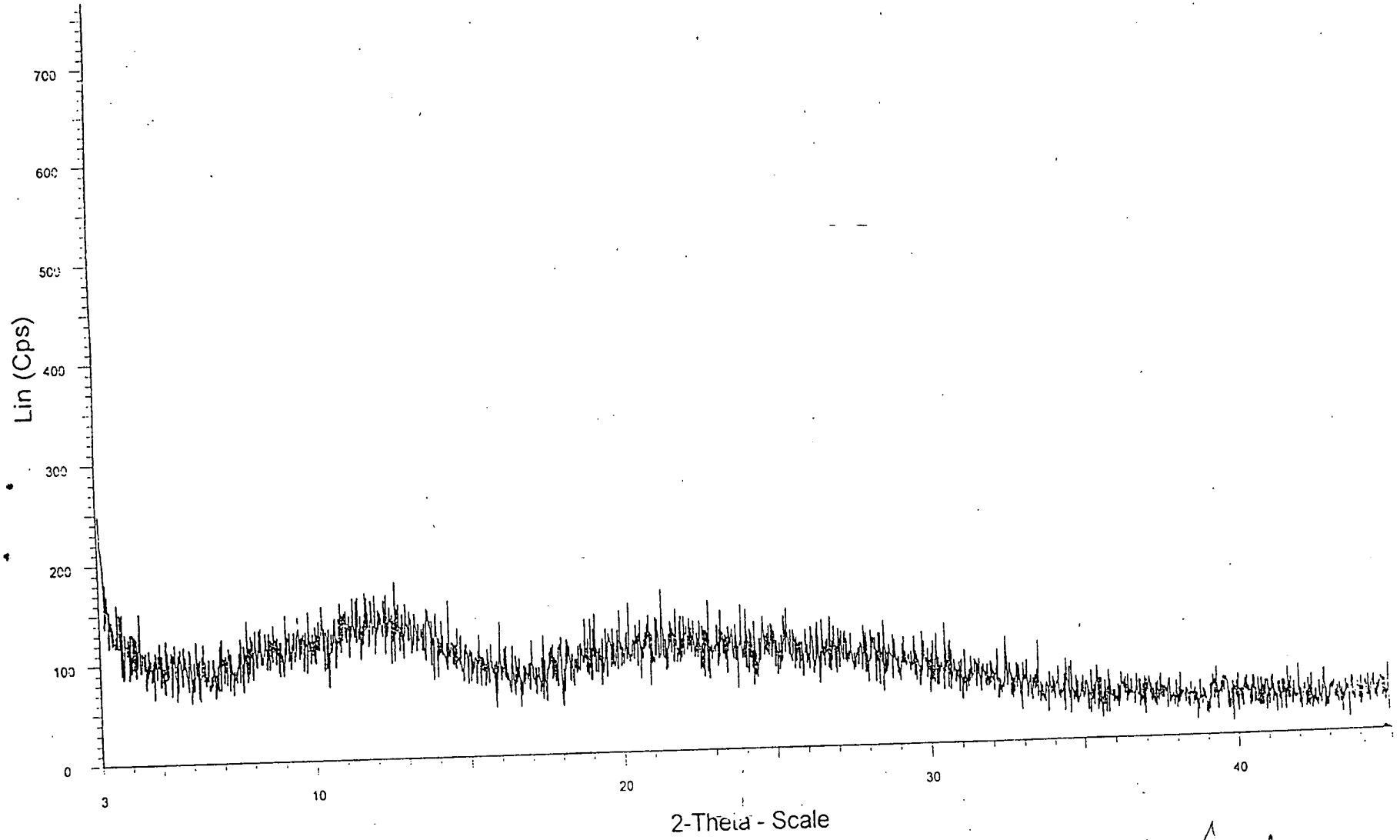


Fig. (1)